



Role of Liver in Heme Synthesis

By

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INTENDED LEARNING OBJECTIVES (ILOs)



By the end of this lecture the student will be able to:

- 1. Outline the structure of porphyrins**
- 2. Illustrate the steps of heme synthesis**
- 3. Discuss regulatory steps of heme synthesis**

Outlines

What is Heme?

Steps of heme synthesis

Regulation of heme synthesis

What is Heme?

?What is Heme

Heme is the *colored prosthetic group* of **hemoglobin** and a number of proteins called **hemeproteins**

Some important heme-proteins

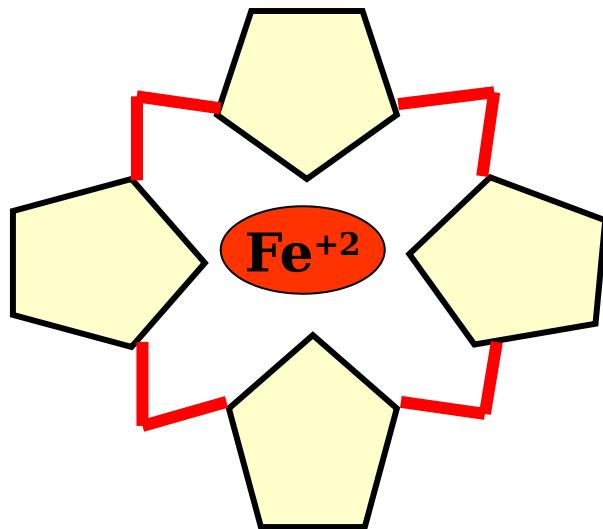
- Electron transport chain cytochromes (cyt aa3, cyt.c)
- Cytochrome P450
- Catalase and Peroxidase (degradation of H₂O₂)
- Tryptophan pyrrolase
- Cytoplasmic guanyl cyclase (activated by

Structure Of Heme

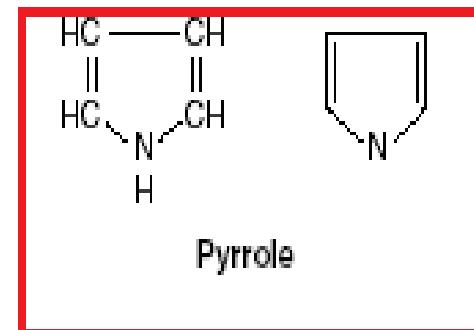
+

porphyrin

Porphyrins = cyclic compounds
formed of four pyrrole rings



Heme group



Pyrrole

Porphyrins

They are **cyclic** compounds

formed of

4 pyrrole rings linked by **methenyl**

They form **bridges**.
complexes with **metal ions** that bind to **Nitrogen** of

:pyrrole rings

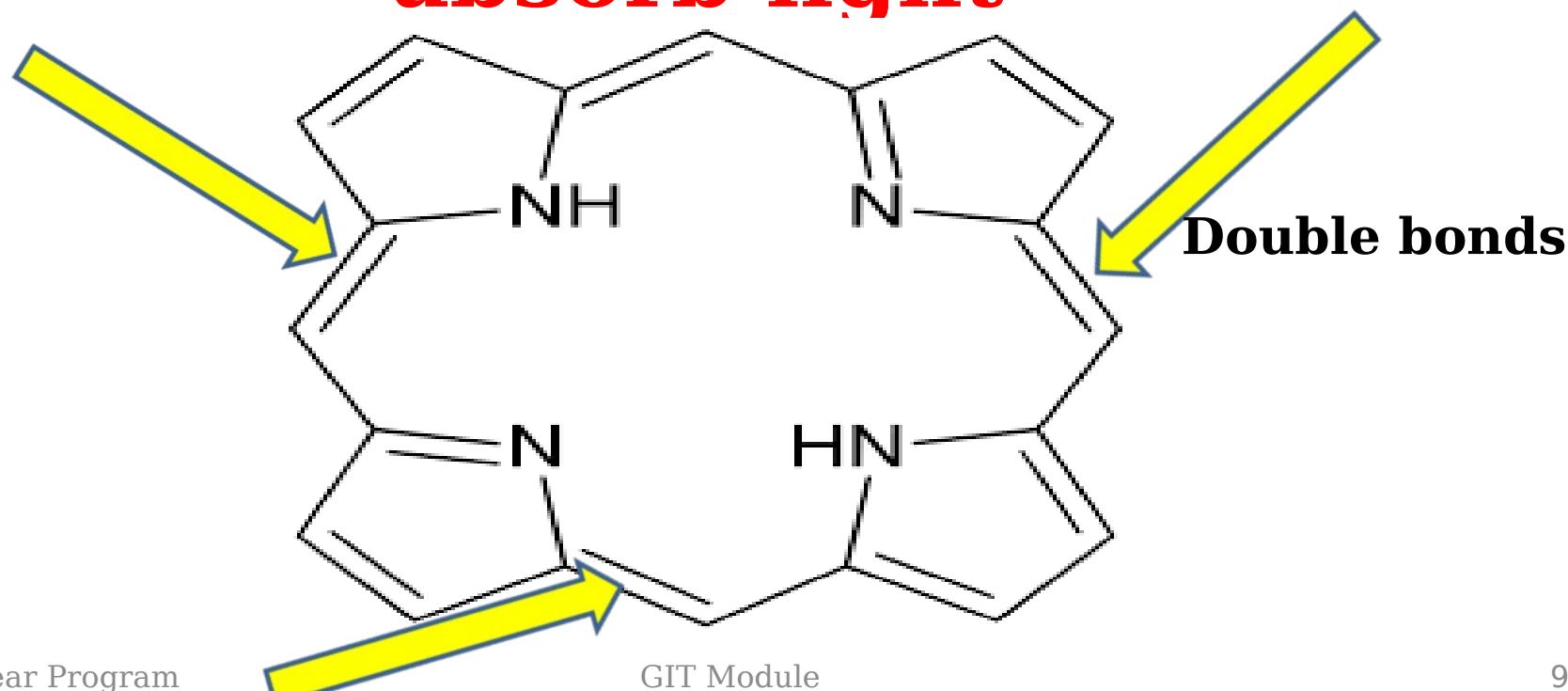
,Iron porphyrins (Heme)

Magnesium porphyrins

Structure Of Porphyrins

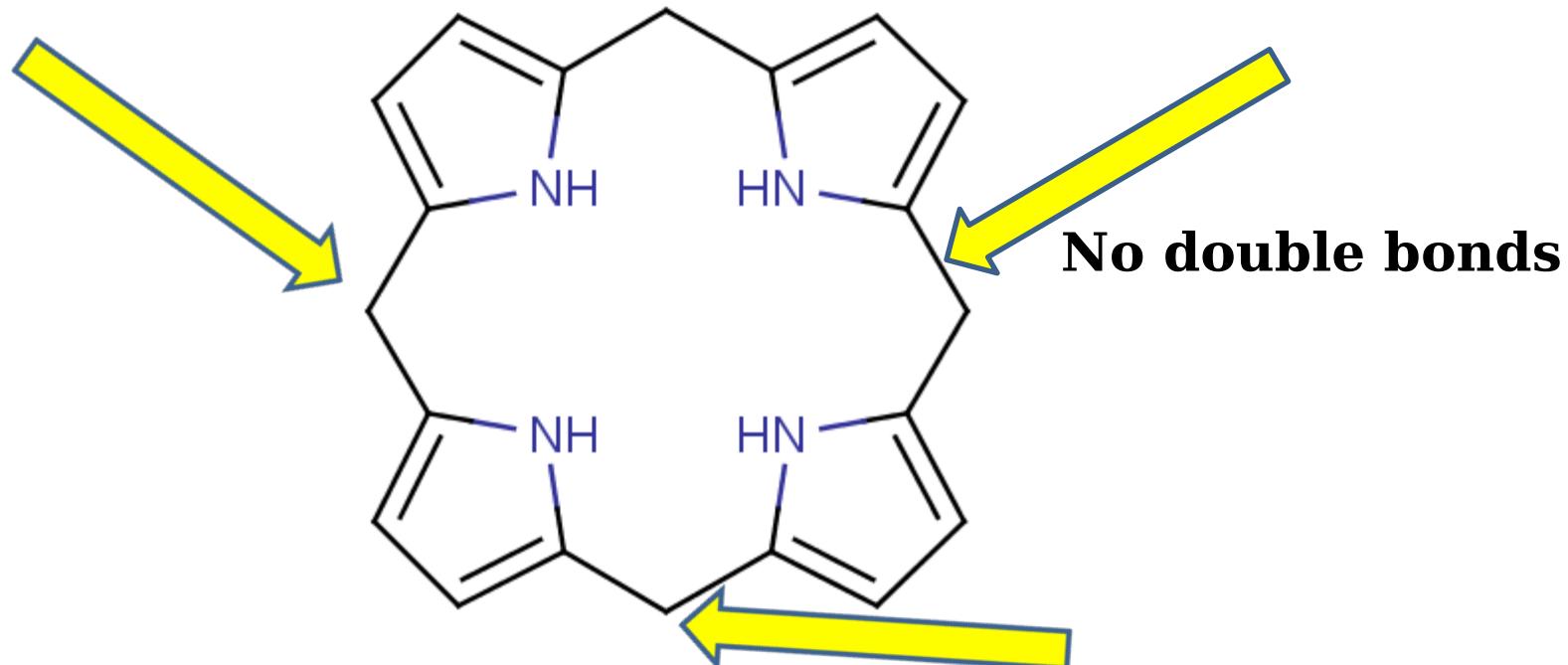
conjugated **double bonds** which

absorb light



Porphyrinogens

They are **reduced** forms of porphyrins that have **no** conjugated **double bonds** and



MCQ

**Porphyrin ring present in all of -1
:the following except**

- A. peroxidase
- B. Xanthine oxidase
- C. Tryptophan pyrrolase
- D. catalase
- E. guanyl cyclase

Steps of heme synthesis

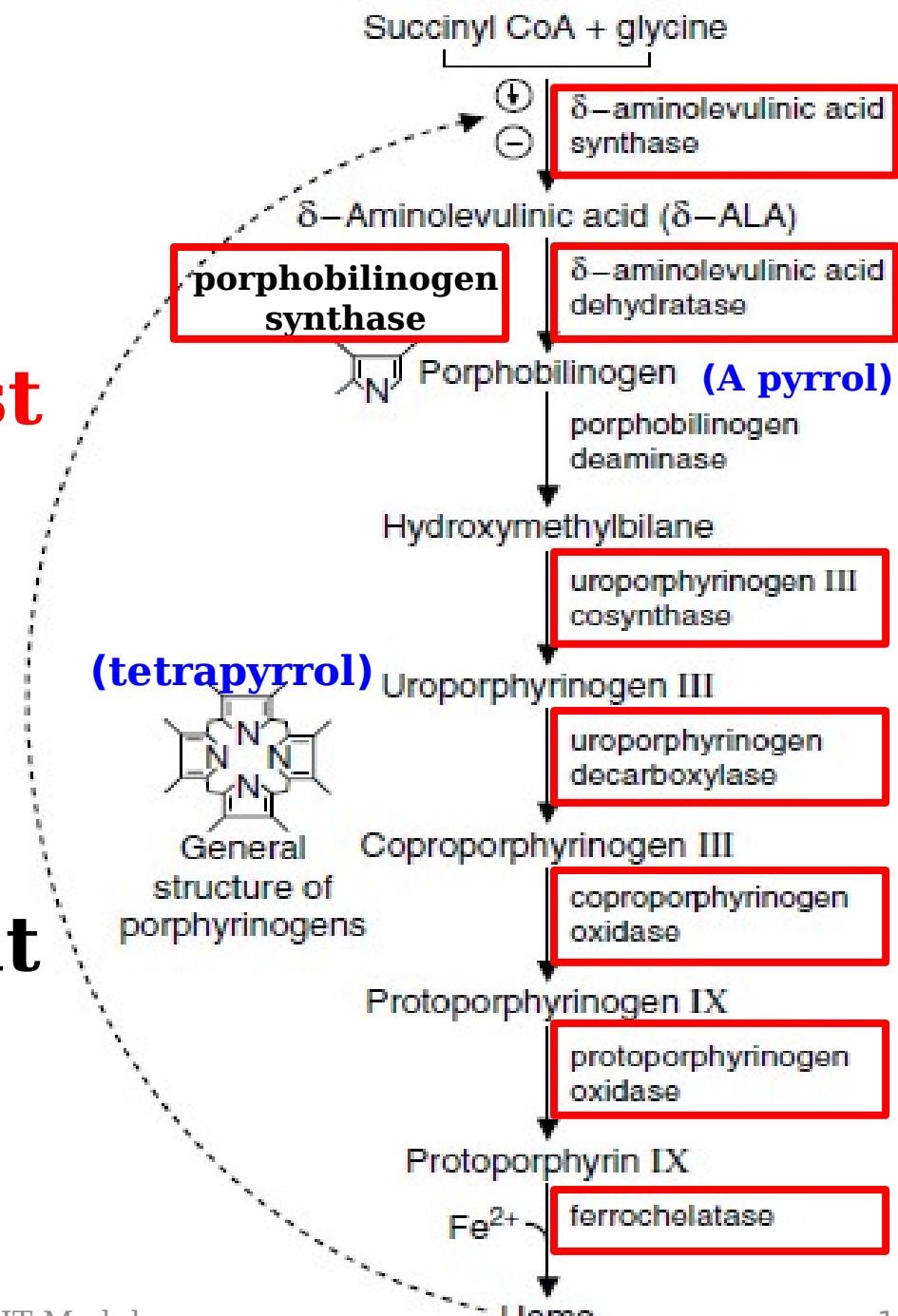
Mainly in the **bone marrow**
(hemoglobin synthesis) and the
liver (cytochrome P450
.synthesis)

Heme biosynthetic pathway is
partly **mitochondrial** and partly
.cytosolic

The reactions are **Irreversible**

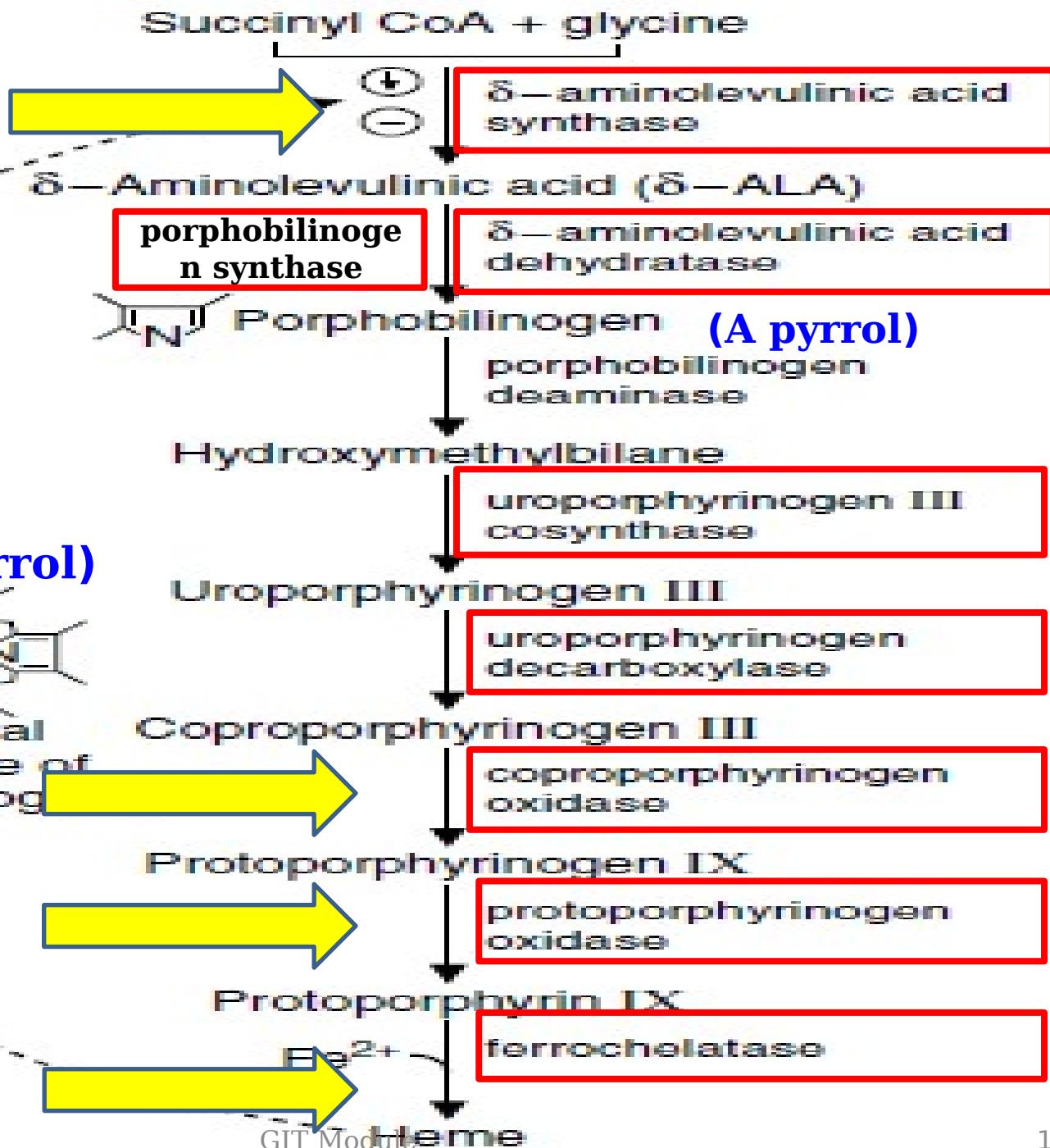
Steps

The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, but the intermediate steps occur in the



Steps

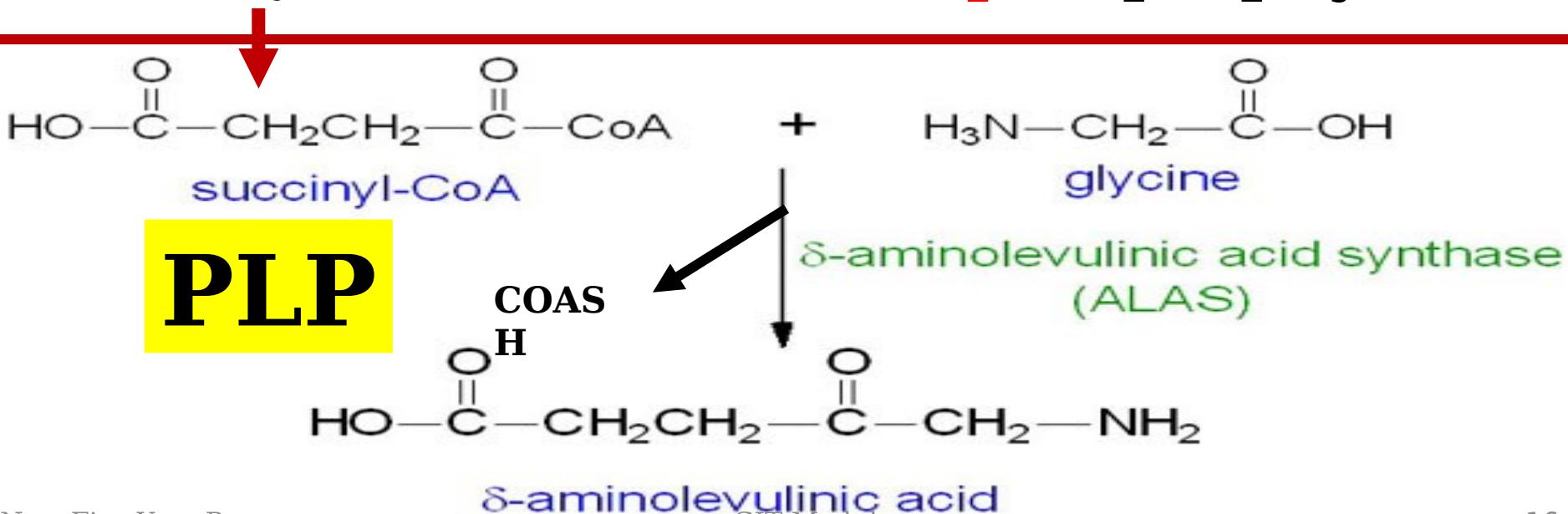
(tetrapyrrol)
General structure of porphyrinogen



Formation of δ -aminolevulinic acid -1 : (ALA)

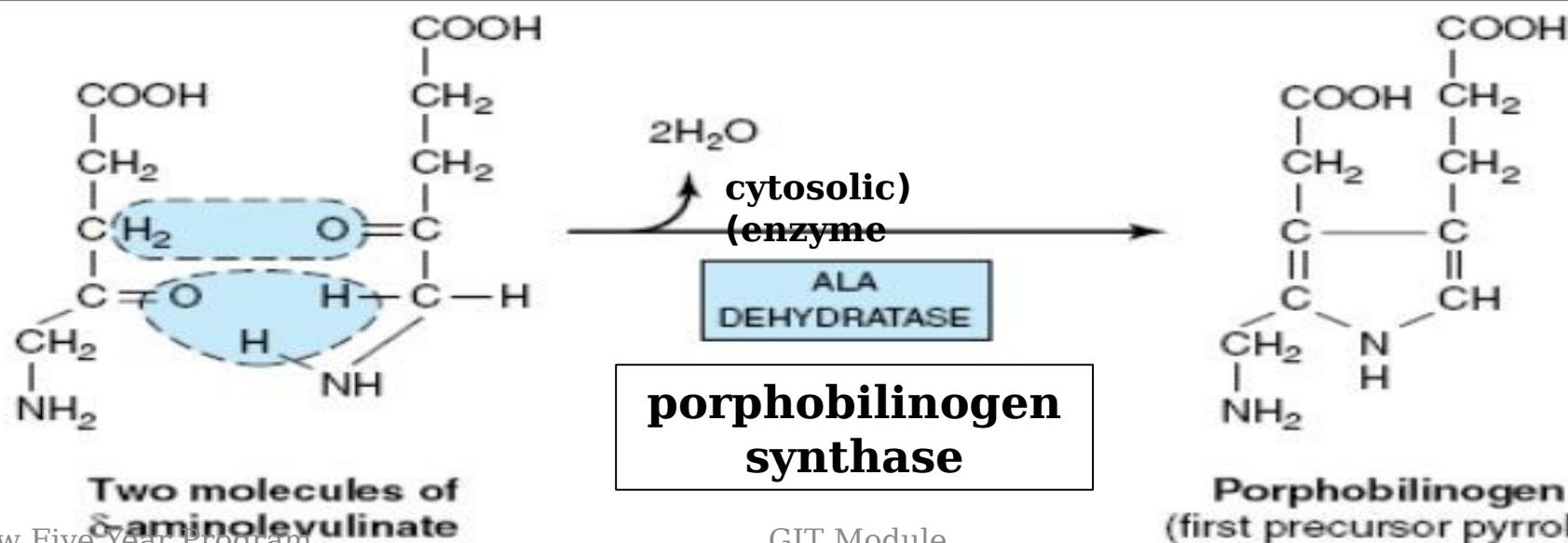
- Glycine and succinyl CoA condense to form ALA by mitochondrial ALA synthase (ALAS).

It is the committed step in porphyrin



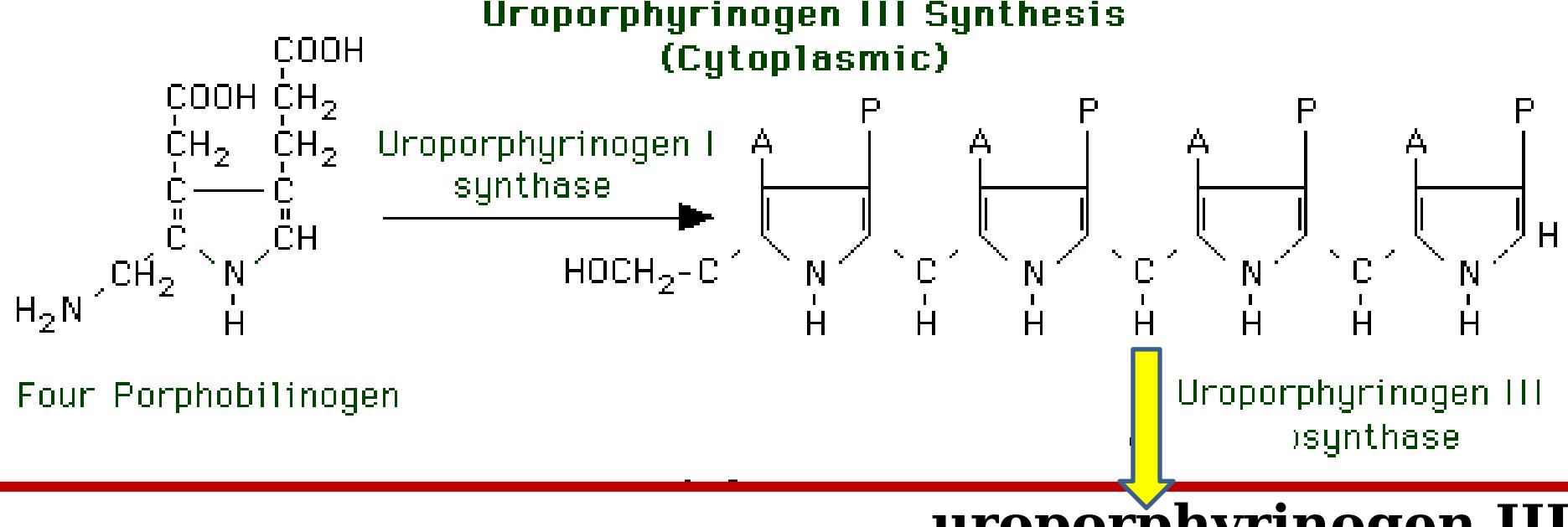
2-Formation of porphobilinogen:

- Condensation of **two** molecules of **ALA** by **Zn-containing cytosolic ALA dehydratase** (porphobilinogen synthase).
- It is **inhibited** by **heavy metal ions** e.g. **lead** that replace the **zinc** .



3- Formation of uroporphyrinogen:

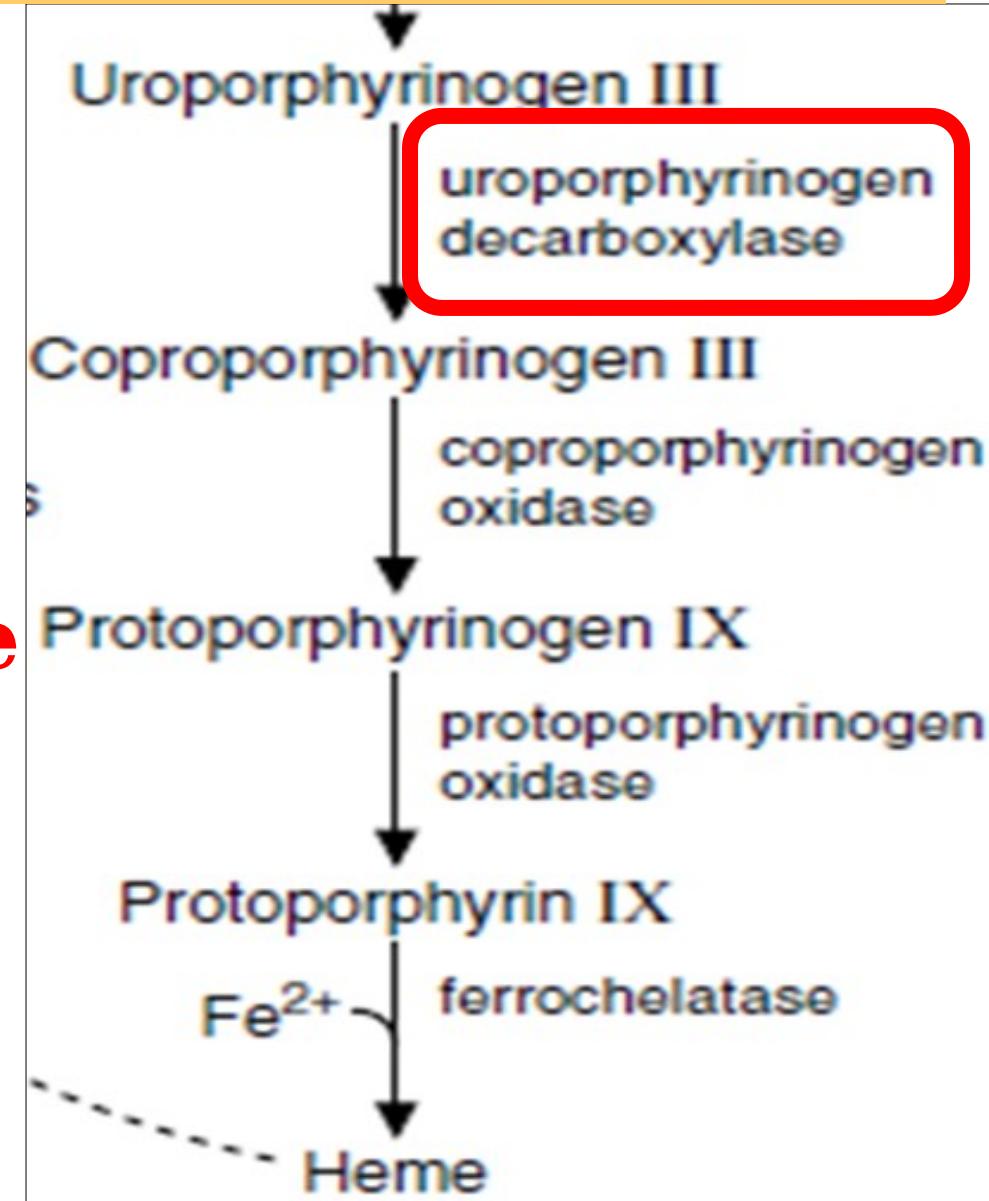
Condensation of **four** porphobilinogens produces a **linear tetrapyrrole**, which is **cyclized** forming **uroporphyrinogen III** by **uroporphyrinogen III Synthase enzyme**



4- Formation of Heme:

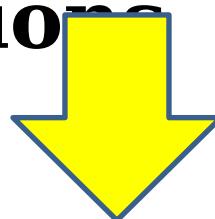
Uroporphyrinogen III undergoes decarboxylation forming coproporphyrinogen III

This reaction occur in the cytosol

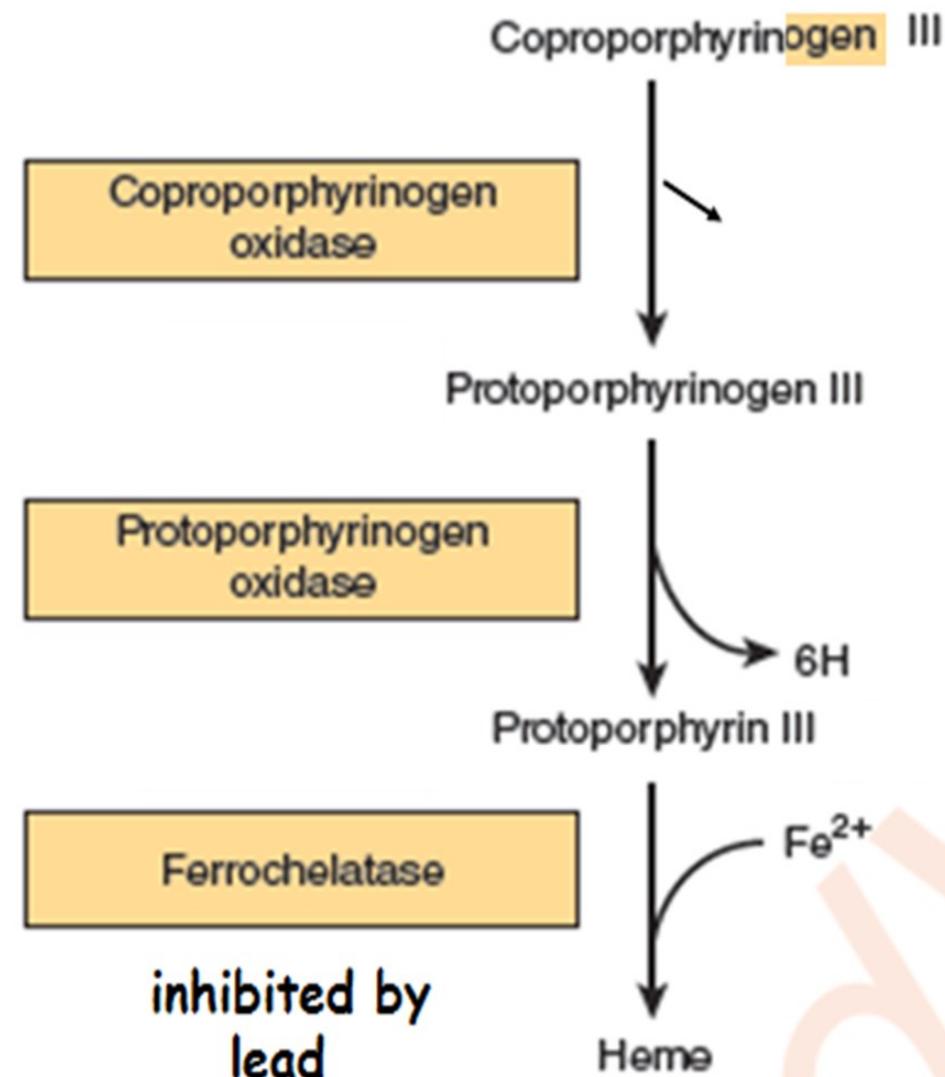


4- Formation of Heme:

Coproporphyrinogen III enters the mitochondrion, followed by oxidation reactions.



Iron (as Fe^{2+}) is introduced into protoporphyrin by ferrochelatase enzyme.



Overall reactions of heme biosynthesis

Glycine + succinyl CoA

←.....

Heme

ALA synthase
(mitochondria)



Delta aminolevulnic acid(ALA)

Protoporphyrin

Ferrochelatase
(mitochondria)

ALA dehydrase
(cytoplasm)



Porphobilinogen

Protoporphyrinogen oxidase
(Ferrochelatase) (mitochondria)



uroporphyrinogen III
Synthase



Uroporphyrinogen III

→

Coproporphyrinogen III

Coproporphyrinogen oxidase
(mitochondria)



Uroporphyrinogen
Decarboxylase (cytoplasm)
GIT Module

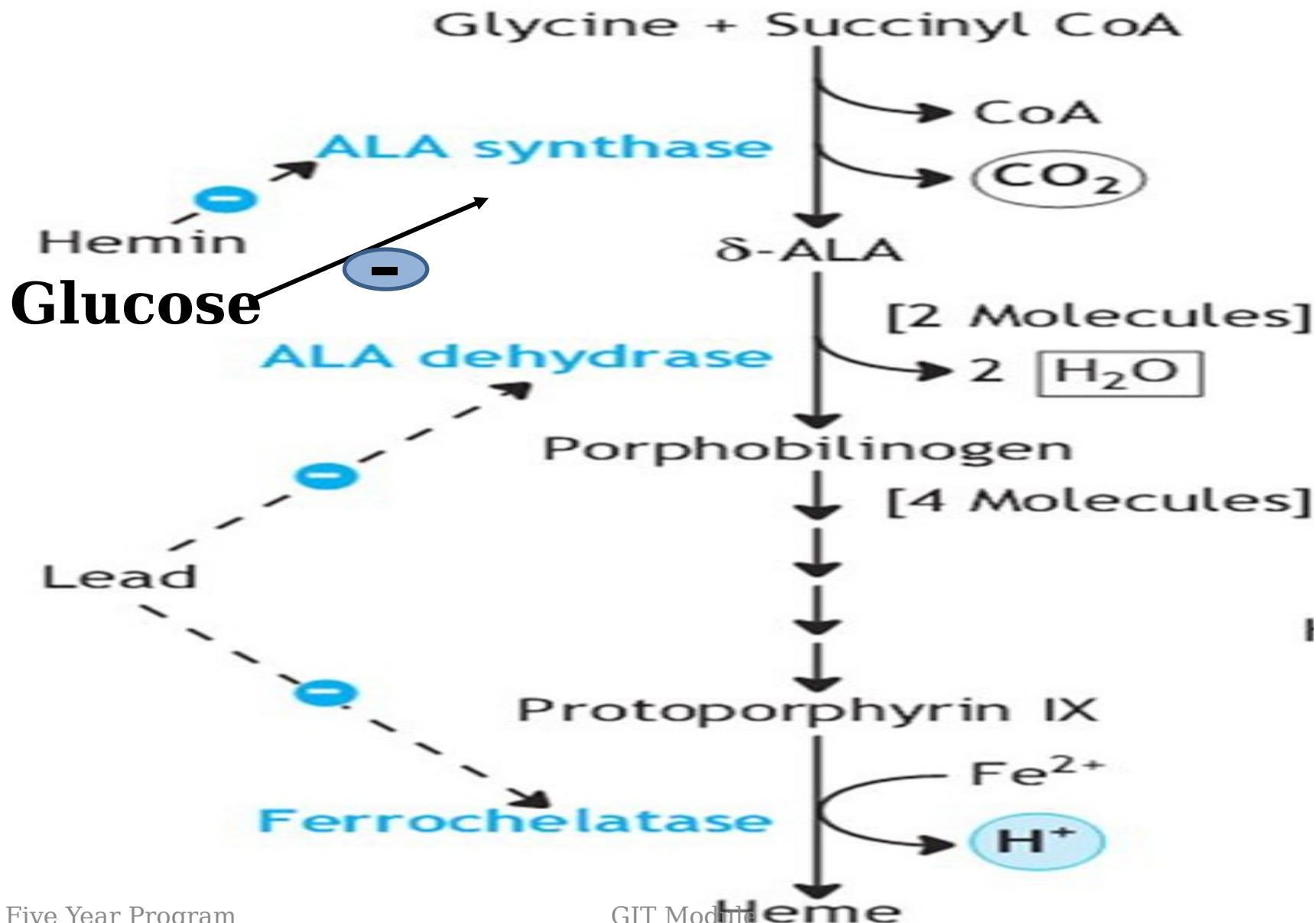
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An amino acid required for -2 :porphyrin synthesis is

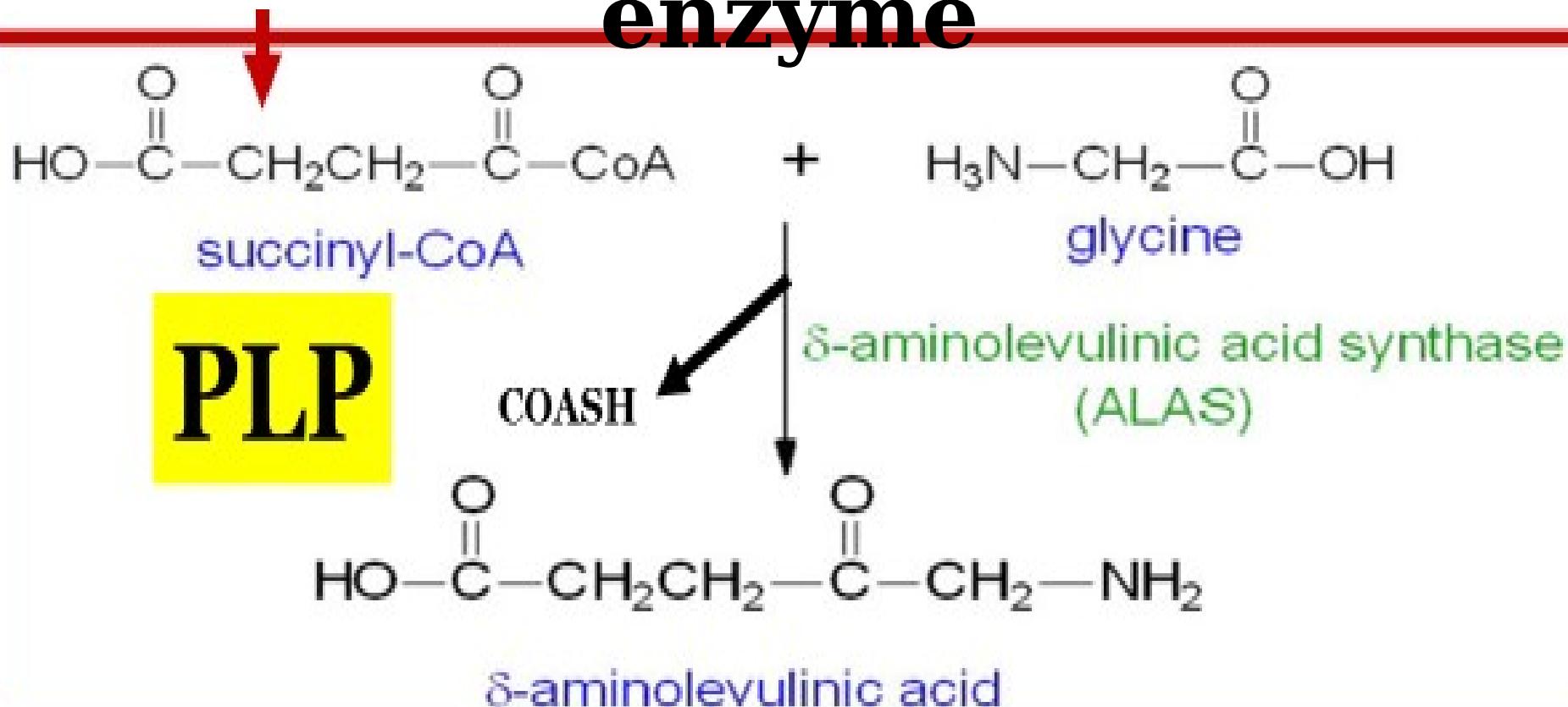
- A. proline
- B. serine
- C. glycine
- D. histidine
- E. alanine

Regulation of heme synthesis

Regulation of Heme Synthesis



ALA synthase is the rate limiting regulatory enzyme



:Effect of heme (hemin) -1

When porphyrin production exceeds the availability of , the apoproteins that require it heme accumulates and is converted to hemin by the . + oxidation of Fe^{2+} to Fe^{3+}

Hemin decreases the amount and the activity of ALAS enzyme

Glycine + Succinyl CoA

ALA Synthase

-

δ aminolevulonic acid (ALA)



HEME

ALA Synthase
catalyzes first step of
heme biosynthesis
Heme end product of
the pathway acts as
allosteric inhibitor

Feed Back inhibition

Effect of drugs (in liver -2 :only)

Drugs metabolized by cytochrome P450 monooxygenase in the liver .

Barbiturates
, alcohol and
carcinogens

↑Synthesis of cytochrome P450

↑Consumption of heme
a component of cytochrome P450 proteins.

↓The concentration of heme in liver
Cells.

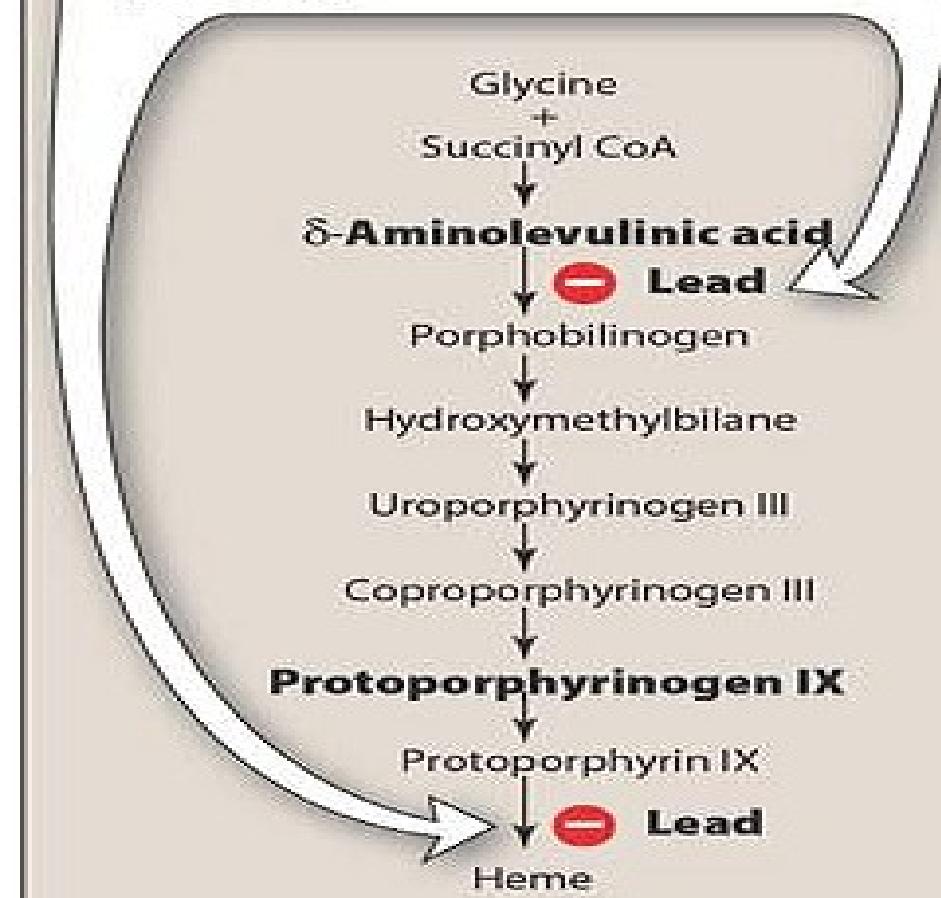
The synthesis of ALAS1 (derepression)

:Effect of Lead -3

Lead has an inhibitory effect on ALA dehydratase & Ferrochelatase

LEAD POISONING

- Ferrochelatase and ALA dehydratase are inhibited by lead.
- Protoporphyrin and ALA accumulate in the urine in lead poisoning.



:Effect of Glucose -4

**Glucose has *inhibitory* effect
on ALA synthase**

MCQ

: **δ -Aminolevulinic acid synthase activity -3**

A. Is frequently decreased in liver in individuals treated with drugs, such as the barbiturate phenobarbital.

B. Catalyzes a rate-limiting reaction in porphyrin biosynthesis.

C. Requires the coenzyme biotin.

D. Is strongly inhibited by heavy metal ions such as lead.

Summary

Heme = Iron in the ferrous state + porphyrin

- The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, but the intermediate steps occur in the cytosol
- ALA synthase is the rate limiting regulatory enzyme

Thank
you



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